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FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,438	WHEELER ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,11 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *4 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,10,11,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2009 has been entered.

Claims 1-7, 10, 11, and 21-26 are pending. Claims 25 and 26 are new. Claims 21-24 remain withdrawn as being drawn to a non-elected invention. Claim 4 remains withdrawn as being drawn to a non-elected species. Claims 1-3, 5-7, 10, 11, 25, and 26 are currently being examined as drawn to the elected species of chemotherapeutic "temozolomide" and species of dendritic cell "primed."

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

NOTE: The rejections below have an added reference, Knutson, and address the new claims and amendments, however, the issues remain essentially the same as the

rejections in the previous Office Action, sections 2 and 3, and Examiner responds to Applicants' remarks below.

2. **Claims 1-3, 5, 10, 11, 25 and 26 are rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent Application Publication 2002/0119121, Vitiello et al, filed 9/6/2001, published 8/29/2002, in view of Knutson (Current Opinion in Molecular Therapeutics, August 2002, 4:403-407) and Friedman et al (Clinical Cancer Research, 2000, 6:2585-2597).

The claims are drawn to a method for treating cancer of the nervous system in a mammal, the method comprising: (a) administering at least one vaccination of dendritic cells (DC) to said mammal suffering from a cancer of the central nervous system; and (b) after (a), administering a regimen of chemotherapy to said mammal, wherein said administering of at least one vaccination of DC occurs prior to administering said regimen of chemotherapy to said mammal, and wherein said regimen of chemotherapy includes the administration of at least temozolomide (claim 1), wherein said DC are primed *ex vivo* (claim 2), wherein said DC are autologous and wherein said DC are tumor antigen-presented DC (claim 3), the method of claim 1, wherein administering said at least one vaccination further comprises administering at least three vaccinations of DC (claim 5), wherein said cancer of the central nervous system and is a glioma, glioblastoma multiforme (claims 10, 11, 25), the method of claim 25 wherein said mammal is a human (claim 26).

Vitiello et al teach a method of treating cancer in a patient (mammalian, human) comprising administering DC to a patient prior to, during, or subsequent to chemotherapy treatment ([2]; [83]; [135]; [140]), wherein the DC are autologous and primed *ex vivo* with tumor antigens from the patient ([36]; [59]; [65-72]; [79-83]; [96]; [99]; [102-103]; [114]), wherein the cancer is a glioma, glioblastoma multiforme ([51]; Table 1).

Vitiello et al does not teach that the chemotherapy is temozolomide or administering DC to the mammal at least three times.

Knutson exemplify treating human patients with glioblastoma multiforme by administering dendritic cells primed *ex vivo* with peptide epitopes from patient glioblastoma multiforme tumor cells, also called "DCVax-Brain" (abstract; p. 403, col. 1-2; p. 404, col. 2, "DCVax-Brain"; p. 405, col. 1). Knutson teach administering the DCVax-Brain in a series of three bi-weekly injections (p. 404, col. 1, "Pharmacology;" p. 404, col. 2, "DCVax-Brain"). Patients receiving DCVax-Brain had a progression rate of 30% while those not receiving DCVax-Brain had a progression rate of 85% (p. 404, col. 2, "DCVax-Brain").

Friedman et al teach successful treatment of glioblastoma multiforme in patients comprising administering temozolomide (abstract; Table 4; p. 2592, col. 1; Fig. 2). Friedman et al teach that combining two or more drugs that have different cytotoxic mechanisms or are subject to different mechanisms of resistance can produce synergistic effects. Temozolomide can be coadministered with various agents (p. 2593, col. 1; p. 2594, col. 1, last para).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use temozolomide as the chemotherapeutic in the method taught by Vitiello et al because Friedman et al teach using temozolomide to treat glioblastoma multiforme. One would have been motivated to use temozolomide as the chemotherapeutic in the method taught by Vitiello et al because Friedman et al demonstrate that temozolomide successfully and safely treats glioblastoma multiforme and expressly suggests combining temozolomide with other agents that use different cytotoxic mechanisms to produce synergistic effects. One of ordinary skill in the art would have a reasonable expectation of success treating glioblastoma multiforme with DC and temozolomide because both agents are known to successfully treat glioblastoma multiforme.

Further, each of the agents, DC and temozolomide, had been taught by the prior art to be used for successfully treating glioblastoma multiforme, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art using DC or temozolomide to treat glioblastoma multiforme, it would have been obvious to combine the two agents for the treatment of glioblastoma multiforme because the idea of doing so would have logically followed from their having been

individually taught in the prior art to be useful as agents for the same purpose of treating glioblastoma multiforme. One of ordinary skill in the art could have combined the two agents and each agent would have performed the same function of treating glioblastoma multiforme as they would have separately. One of ordinary skill in the art would have recognized the results of such a combination of agents as predictable.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the DC at least three times because Knutson teach this administration regimen is used in human subjects for treatment of glioblastoma multiforme. One would have been motivated to use this administration regimen in order to treat glioblastoma multiforme by eliciting a cytotoxic T-cell response to the tumor. One of ordinary skill in the art would have a reasonable expectation of success using this administration regimen because Knutson demonstrate it can be successfully and safely administered to glioblastoma multiforme patients for treatment and reduce the progression rate.

Response to Arguments

3. Applicants argue that *Kerkhoven* did not relate to unpredictable methods of medical treatment. Applicants argue that the claims at issue in *Kerkhoven* were directed to predictable processes for producing detergent mixtures. Applicants argue that the dissent points out that "the uncertainty and unpredictability often associated with the chemical arts is not present here." 204 USPQ at 1075. Applicants argue that because one skilled in the art would not have been able to predict that administration of

chemotherapy after a DC vaccination would have significantly improved survival or time to recurrence as compared to chemotherapy without vaccination, the reasoning of *Kerkhoven* is not relevant to the instant claims (p. 5).

The arguments have been considered but are not found persuasive. With regards to predictability or certainty, treating glioblastoma with either DC or temozolomide were known and predictable methods of treatment of glioblastoma in the art, therefore they are not uncertain or unpredictable methods for treating glioblastoma as Applicants are arguing. The analysis of *Kerkhoven* is relevant to the instantly claimed method because it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Arguments with regards to significantly improved results for survival or time to progression are addressed by Examiner below.

4. Applicants argue that there is a long-felt but unsolved need for effective central nervous system (CNS) cancer therapies, and that Applicants have provided evidence of unexpectedly beneficial results in the battle against these devastating forms of cancer. The instant specification teaches that "GBM [glioblastoma multiforme] diagnosis carries with it an average survival between twelve and eighteen months (with 90-95% [of] patients surviving less than two years), without the possibility of spontaneous remission or effective treatment" ([0004]). Applicants argue that Stupp et al teach that "[d]espite

advances in surgery and radiotherapy, [malignant glioma] tumors will invariably recur with an ultimately fatal outcome" (abstract). Stupp et al further state that "[a] systematic and integrated approach in developing new treatment modalities and translational research is required for clinically relevant advances in this disease" (abstract). Applicants argue that at the time of the present application, there was a need for life-extending therapies for CNS cancer, and in particular for GBM (p. 6).

The arguments have been considered but are not found persuasive. Applicants have not shown how the long-felt need for treatment of glioblastoma was not solved previously or by the teaching of the combined references. For example, as stated in the rejection above, Knutson teach DCVax-Brain reduced the progression rate of glioblastoma from 85% to 30%. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP §716.04.

5. Applicants argue that in view of the unpredictability inherent in therapy for cancer of the central nervous system and the long-felt need for improved therapeutics, Applicants' experimental results described in the specification are surprising. As described in Examples 1 and 2 of the application, newly diagnosed GBM patients were administered surgical resection and standard radiation therapy, followed by either administration of chemotherapy or vaccination with DCs ([0044], Fig. 1A). Both the vaccine and chemotherapy groups had similar times of progression to an initial disease

recurrence ([0046], Fig. 1B). Following an initial recurrence, patients in the vaccine + chemotherapy group were then administered a course of chemotherapy (see Fig. 1A). Applicants argue that the average time to subsequent recurrence in patients administered chemotherapy following vaccination (about 13 months) was significantly increased compared to both initial recurrence in all groups (about 7-8 months) and the subsequent recurrences in the vaccine (about 6 months) and chemotherapy (about 3 months) groups (see Fig. 1B). Applicants argue that administration of chemotherapy following vaccination provided a significant delay in progression of the disease as compared to chemotherapy or vaccination alone (p. 6).

The arguments have been considered but are not found persuasive. Although Applicants argue that the average time to subsequent recurrence in patients administered chemotherapy + vaccination was significantly increased compared to subsequent recurrences in vaccine or chemotherapy groups and that this result is surprising, Examiner argues that the result of combining chemotherapy + DC vaccine is an expected beneficial and synergistic result for the treatment of glioblastoma and is not surprising in view of the prior art: 1) Vitiello et al teach DC can be administered to a patient prior to, during, or subsequent to chemotherapy treatment; 2) Knutson demonstrate the significant increase in time to progression using DC alone, wherein patients receiving DCVax-Brain had a progression rate of 30% while those not receiving DCVax-Brain had a progression rate of 85%; and 3) Friedman et al demonstrate that temozolomide successfully and safely treats glioblastoma multiforme and expressly suggests combining temozolomide with other agents that use different cytotoxic

mechanisms to produce synergistic effects. Given these facts known in the prior art, the result of combining two different modes of treatment, both known to successfully treat glioblastoma and with significant results, yields expected beneficial results for treating glioblastoma (hence, not surprising or unpredictable) and yields expected synergistic effects. Further, the instant specification discloses that there was NO significant difference in survival between the vaccine + chemotherapy group and vaccine group (Figure 2; [00010], last sentence). Given the data presented by Knutson demonstrating significant results with DC vaccination alone for glioblastoma treatment, and given the data in the specification demonstrating no significant difference in survival between vaccine + chemotherapy group and vaccine group for glioblastoma patients, the significant improvement in treatment resulting from combining the DC vaccine of Vitiello et al and Knutson with the temozolomide of Friedman et al is not surprising or unexpected.

MPEP 716.02(c) states "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). As stated above, the combination of two successful modes of treatment for the same purpose of treating glioblastoma yield expected beneficial results.

Further, with regards to significant results or greater than additive results argued by Applicants for time to progression for the vaccine + chemotherapy group (Figure 1B) MPEP 716.02(a) states "a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be

expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991)." As stated above, the art teaches that administering DC vaccine alone provides significant increases in survival (Knutson above), and Friedman et al demonstrate that temozolomide successfully and safely treats glioblastoma multiforme and expressly suggests combining temozolomide with other agents that use different cytotoxic mechanisms to produce synergistic effects, therefore there is an expectation in the art for significant and synergistic effects for glioblastoma treatment when combining DC vaccine and chemotherapy, temozolomide. Again, it is noted that the instant specification demonstrates there is no statistically significant difference in survival time for glioblastoma patients treated with the vaccine alone or the vaccine + chemotherapy (Figure 2; [0010]).

Finally, as stated before, the art provides an expectation of beneficial results and synergistic effects for glioblastoma treatment when combining DC vaccine with chemotherapy, temozolomide. Although Applicants argue that it is the administration of a specific sequence of DC vaccine followed by chemotherapy that results in significant and unexpected results for glioblastoma treatment, neither the specification nor Applicants provide comparisons of treatment of glioblastoma patients with simultaneous vaccine + chemotherapy treatment or chemotherapy followed by vaccine treatment to indicate that it is the sequence of administration alone that provides significant results or if it is simply the combination of treatment that provides significant and beneficial

results. The method taught by the combined references above render obvious the instantly claimed invention for the reasons of record.

6. Applicants argue that GBM patients receiving chemotherapy after vaccination enjoyed significantly prolonged survival relative to patients receiving either treatment individually ([0045], Figs. 2 and 5). Applicants argue that the mean survival of the vaccine + chemotherapy group was significantly longer (26 + 3.7 months) as compared to the mean survival of the either the vaccine only or chemotherapy only group (17.9 + 1.7 and 15.9 + 2.1 months, respectively). Applicants argue that some patients administered the sequential therapy survived for three or four years, whereas there were no three- year survivors in the vaccine or chemotherapy group ([0048]). In addition, tumor regression was observed in three of the thirteen patients receiving the vaccine and chemotherapy treatment, apparently the first demonstration of objective regression in an adoptive immunotherapy setting ([0047]). In view of the teaching of the specification that "GBM diagnosis carries with it an average survival between twelve and eighteen months (with 90-95% [of] patients surviving less than two years), without the possibility of spontaneous remission or effective treatment," Applicants argue that these findings of increased survivorship and tumor regression are remarkable. Applicants argue that the increase in life by an average of eight months compared to other therapies is a significant, and unexpected, improvement in therapy for GBM (p. 6-7).

The arguments have been considered but are not found persuasive. As stated above, and contrary to Applicants' assertion, the specification discloses that there was NO statistically significant difference in survival time between the vaccine + chemotherapy and the vaccine only group (see paragraph [0010], last sentence). The prior art of the combined references (Vitiello et al, Knutson, and Friedman et al) provide an expectation of beneficial results and synergistic effects for glioblastoma treatment when combining DC vaccine with chemotherapy, temozolomide, for the reasons set forth above. Further, Knutson demonstrate that treatment with DC vaccine is successful and reduced progression rate to 30% compared to 85% for untreated patients, therefore increased survivorship is expected. Although Applicants argue the instant specification discloses the first demonstration of objective regression in an adoptive immunotherapy setting, Osada et al (Jpn J Clinical Oncology, 2001, 31:403-406) demonstrate successful brain tumor regression in a patient treated with a DC vaccine (Figure 3) and Kikuchi et al (Cancer Immunol Immunother, 2001, 50:337-344) demonstrate successful regression of a GBM tumor after administration of a DC vaccine to a patient (p. 341, col. 1, case 1 patient), therefore the prior art demonstrates that DC vaccines are already known to induce brain tumor regression and this result is not surprising or unexpected.

7. Applicants argue that a comparison between treatment groups of vaccine before chemotherapy and chemotherapy before vaccine is not required to establish surprising results. Applicants argue that a comparison is inherent in the data presented and point to Fig. 5, stating that about one-third of the patients in the vaccine and the vaccine +

chemotherapy group had received some form of chemotherapy prior to vaccination. Applicants argue that if there were an additive or synergistic effect of administration of chemotherapy prior to vaccination, one might expect to have seen some advantage of the vaccine group as compared to the chemotherapy group. However, the time to initial recurrence for the vaccine group was not significantly different from that of patients in the chemotherapy group (Fig. 1B). Additionally, median survival was also not significantly different between the vaccine and chemotherapy groups (Fig. 2, Fig. 5). Applicants argue that the only significant difference observed was when chemotherapy was administered following vaccination. Applicants argue that administration of chemotherapy following an initial recurrence clearly extended the time to subsequent recurrence in the vaccine + chemotherapy group as compared to the vaccine only or chemotherapy only groups (Fig. 1B) and also increased overall survival (Fig. 2, Fig. 5) (p. 7-8).

The arguments have been considered but are not found persuasive. First, it is noted that 33% of the vaccine group (4 out of 12) and 38% of the vaccine + chemotherapy group (5 out of 13) received prior chemotherapy, therefore it appears there would not be any advantage for the vaccine only group because the vaccine + chemotherapy group has nearly the same (slightly greater) percentage of patients with prior chemotherapy, hence Applicants' logic is unclear. It is also noted again that there was no statistically significant difference in survival times for both the vaccine group and vaccine + chemotherapy group.

Second, the specification discloses that DC vaccine is administered to GBM patients at diagnosis followed by chemotherapy administration *at the time of recurrence*. This is the data that Applicants consistently point to for their arguments of significant results. Therefore, the specification indicates that chemotherapy administered at a specific time post-DC vaccination (time of recurrence) was critical to increasing the time to tumor progression, however **the claims do not recite this limitation.** The claims are broadly drawn to administration of chemotherapy *anytime after DC vaccination*.

MPEP 716.02(d) states: Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Claims were directed to a process for removing corrosion at "elevated temperatures" using a certain ion exchange resin (with the exception of claim 8 which recited a temperature in excess of 100C). Appellant demonstrated unexpected results via comparative tests with the prior art ion exchange resin at 110C and 130C. The court affirmed the rejection of claims 1-7 and 9 10 because the term "elevated temperatures" encompassed temperatures as low as 60C where the prior art ion exchange resin was known to perform well. The rejection of claim 8, directed to a temperature in excess of 100C, was reversed.).

Similarly, the instant application demonstrates significant increases in time to progression for patients who received DC vaccine followed by chemotherapy

administered *at the time of recurrence*, however, the specification does not demonstrate significant results for GBM treatment for chemotherapy administration anytime after DC vaccination, nor does the specification or art provide comparisons with treatment groups comprising vaccine after chemotherapy or simultaneous chemotherapy + vaccine administration, therefore specification does not provide significant or unexpected results for the entire claimed range of chemotherapy administration anytime after DC vaccination. The combined references (Vitiello et al, Knutson, and Friedman et al) provide an expectation of beneficial results and synergistic effects for glioblastoma treatment when combining DC vaccine with chemotherapy, temozolomide, for the reasons set forth above.

8. **Claims 6 and 7 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Application Publication 2002/0119121, Vitiello et al, filed 9/6/2001, published 8/29/2002, Knutson (Current Opinion in Molecular Therapeutics, August 2002, 4:403-407), and Friedman et al (Clinical Cancer Research, 2000, 6:2585-2597) as applied to claims 1-3, 10, 11, 25, and 26 above, and further in view of Liu et al (J of Immunotherapy, July/August 2003, 26:301-312).

The claims are drawn to the method of claim 1, wherein each of said at least one vaccination comprises from about 10^5 to about 10^7 DC (claim 6), wherein each of said at least one vaccination of DC comprises about $10X10^6$ to about $40X10^6$ DC (claim 7).

Vitiello et al, Knutson, and Friedman et al teach a method of treating glioblastoma multiforme in a human comprising administering at least one or three vaccinations of DC to said human and administering a regimen of temozolomide chemotherapy after DC administration as set forth above.

Vitiello et al, Knutson, Friedman et al (the combined references) do not teach each of said at least one vaccination comprises from about 10^5 to about 10^7 DC, or about $10X10^6$ to about $40X10^6$ DC.

Liu et al teach a method of treating glioblastoma multiforme in a patient comprising administering autologous DC primed *ex vivo* with tumor antigen at a dose of $10X10^6$ to $40X10^6$ three times (p. 308, col. 2). Several of the patients produced a cytotoxic T-cell response to their own tumor cells *in vitro* (p. 310, col. 2; p. 311, col. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the DC in the method taught by the combined references at dosages of $10X10^6$ to $40X10^6$ because Liu et al teach this dose can be safely used in subjects for treatment of glioblastoma multiforme. One would have been motivated to use this dose in order to treat glioblastoma multiforme by eliciting a cytotoxic T-cell response to the tumor. One of ordinary skill in the art would have a reasonable expectation of success using this dose because Liu et al demonstrate it can be successfully and safely administered to glioblastoma multiforme patients to elicit a cytotoxic T cell response for treatment.

Response to Arguments

9. Applicants argue Liu et al is not sufficient to overcome the deficiencies of Vitiello et al and Friedman et al as discussed above with regards to unpredictability of treating CNS cancer, long-felt need for effective treatments, and surprising results (p. 8).

The arguments were considered above and are not found persuasive for the reasons set forth above.

10. **Conclusion:** No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642